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NOSOCOMIAL INFECTIONS DUE TO DRUG RESISTANT GRAM NEGATIVE BACTERIA: FRIENDS TURNED FOE

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ABSTRACT

Nosocomial infections are commonly associated with invasive medical devices or surgical procedures. The emergence of multi-drug resistance organisms particularly the Gram-negative bacteria creates a challenge in the treatment of nosocomial infections. The emergence of multidrug-resistant (MDR) Gram-negative bacteria in the healthcare is a serious concern. Compounding the problem of antimicrobial resistance is the immediate threat of a reduction in the discovery and development of new antibiotics. Recent clinical attention has focused on the increasing frequency of Gram –negative pathogens responsible for hospital acquired infections (HAIs), e.g. extended- spectrum β-lactamase (ESBL) and carbapenemase producing Enterobacteriaceae, in particular *A. baumannii* have caused major challenges recently. The treatment options have been limited to two revived old antibacterial (colistin and fosfomycin), a newer one (tigecyclin) and an improved of an existing class (doripenem) are the therapeutic left. The multi-factorial causes of nosocomial infections has to be addressed, inclusive of the use of antibiotics in animals as wells in humans.

KEYWORDS: Nosocomial Infection, Multidrug, Resistant, Gram, Negative Bacteria, Bloodstream Infection

INTRODUCTION

Sulfonamides were introduced in 1930s and antimicrobials in 1940s, resistance to these drugs appeared at the same time. The problem of multiple drug resistant strains of *Shigella* was first observed in Japan. By 1959; approximately 50% of *shigella* isolates showed this pattern of multi-drug resistance, these multiple-drug resistance strains could transfer the gene conferring drug resistance to other antibiotic sensitive strains such as *Escherichia coli* [1]. Most *E. coli* strains reside harmlessly in the lumen of colon seems to be poorly adapted to cause disease in healthy adults. Pathogenic strains differ from commensal organisms in that they produce virulence factors specific for each pathotype, which may be encoded by bacteriophages, or plasmids, or on stretches of chromosomes known as pathogenicity islands. Most pathogens have larger genomes than do the nonpathogenic strains It is estimated that total "pangenome" of *E. coli* consists of more than 13000 genes [2, 3]. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death. Hospital acquired infections are caused by methicillin resistant *Staphylococcus aureus* (MRSA) and multidrug resistant Gram-negative bacteria [4]. In U.S, it is estimatedthat in 2002, a total of 1.7 million hospital acquired infections (HAI) occurred and almost 99,000 deaths resulted or were associated with HAIs [5]. Approximately one third or more of HAIs are preventable [6]. Compounding the problem of antimicrobial-drug resistance is the immediate threat of a reduction in the discovery and development of new antimicrobics [7]. Recent clinical attention has focused on the increasing frequency of Gram-negative pathogens responsible for HAIs .In this group, extended-spectrum β-lactamase (ESBL) and carbapenemase producing Enterobacteriaceae, in particular *E. coli*, *K. pneumoniae*, as well as carbapenemase producing *A. baumannii* have caused major challenges in the past decade [8]. The emergence of multidrug-resistant (MDR) Gram-negative bacilli creates a challenge in the treatment of nosocomial infections. While the pharmaceutical pipeline is waning, two revived old antibacterial (colistin and fosfomycin), a newer

one (tigecycline) and an "improved" of an existing class (doripenem) are the therapeutic left [9]. This article reviews the nosocomial infections due to multidrug-resistant Gram-negative bacteria.

HOSPITAL ACQUIRED INFECTIONS-HAIs

Hospital acquired infection or nosocomial infections are most commonly associated with invasive medical devices or surgical procedures. Lower respiratory tract and bloodstream infections are the most lethal; however, urinary tract infections are most common. Recent data from the U.S. National Healthcare safety Network indicate that gram-negative bacteria are responsible for more than 30% of HAIs, and these bacteria predominate in cases of ventilator-associated pneumonia (47%) and urinary tract infections (45%) [10]. In intensive care units (ICUs) in the United States, gram negative bacteria account for about 70% of these types of infections, and similar data reported from other parts of the world [11]. A range of gram-negative organisms are responsible for HAIs, the Enterobacteriaceae family being the most commonly identified group overall. Other multidrug-resistant organisms, including *pseudomonas aeruginosa*, *Acinetobacterbaumannii*, and extended spectrum β lactamase (ESBL)-producing or carbapenemase- producing Enterobacteriaceae, are increasingly being reported worldwide.

EMERGENCE OF ANTIMICROBIAL RESISTANCE

Researchers in Japan reported the drug resistant strains, able to transfer their resistance determinants, have been discovered in most countries of the world including Australia. The R factors can be classified into two groups depending on whether their drug resistance determinants are able to exist as part of transfer factor or as an independent replicon within the cell. Abundant examples of both types have been found and either type may specify resistance to as a single drug or many different drugs (resistance to 11 different drugs being conferred by a isolated R factor). Drug resistance factors have been found in a wide variety of genera including *Salmonella, Shigella, Proteus, Escherichia coli, Pseudomonas, Klebsiella, Serratia* and in vitro transfer has demonstrated to *Vibrio and Yersinia. O*pportunistic Gram-negative pathogens such as *Pseudomonas, Proteus, Klebsiella, Serratia*and *Escherichia coli* has been involved in fatal cases of septicemia amongst seriously ill hospital patients. In general, these strains exhibit resistance to most if not all of the antibiotics available for therapy [12, 13]. Outbreaks of typhoid fever in Mexico, India and Vietnam have involved strains of *Salmonella typhi* possessing transmissible drug resistance determinants specifying resistance to chloramphenicol, streptomycin, tetracycline, and sulfonamides. More than 10,000 cases occurred in Mexico. There have also been reports of strains of *Salmonella typhimurium* causing serious problems in pediatric wards in Central and South America. In these outbreaks the strains were resistant to chloramphenicol streptomycin, sulfonamides, tetracycline, kanamycin and ampicillin and case mortality reached 20%. A detailed study of R factor mediated resistance has revealed that in the case of many antibiotics, resistance is caused by enzymes which specifically alter the chemical structure of the drug and destroy its selective toxicity [14].

The development of antimicrobial resistance (AMR) is a natural phenomenon .However; certain human actions actually accelerate the emergence and spread of AMR. AMR is a complex problem driven by many interconnected factors so single, isolated interventions have little impact and coordinated actions are required. Underlying factors that accelerate the emergence and spread of AMR include: lack of a comprehensive and coordinated responses; weak or absent antimicrobial resistance surveillance and monitoring system; inadequate systems to ensure quality and uninterrupted supply of medicine; inappropriate use of antimicrobial medicines, including in animal husbandry; poor infection prevention and control practices; insufficient diagnostic, prevention and therapeutic tool; fostering coordinated actions by all stakeholders; creating policy guidance, support for surveillance, technical assistance, knowledge generation and

partnerships, and fostering innovation, research and development [4].

DRUG RESISTANT GRAM NEGATIVE BACTERIA

Two types of cephalosporinases commonly described in human and animal pathogens are ESBLs and CMY-2 type of resistance was commonly described in *Salmonella* and *E. coli* isolated from food producing animals [15, 16]. CMY-2 producing *E. coli* is also relatively common in humans and nearly as common as ESBL producing *E. coli* [17]. Nowadays, CTX-M type ESBLs are the most commonly reported beta-lactamases both in humans and animals. Until the year 2000, TEM and SHV type ESBLs were of great concern and mostly in *E. cloacae* and *K. pneumoniae*. However since mid-2000s, there has been a dramatic shift into the predominance of CTX-M type ESBLs [18,Hanna,8].In the USA, CTX-M type ESBL, mostly CTX-M-15 occurred at rate of 7.3% amongst *E. coli* causing urinary tract infection in dogs [19,Hanna,10].CTX-M producing *E. coli* was quite common in pig farms in China with prevalence of 10.7% [20]

E. coli is the leading cause of urinary tract infections in humans and dogs. *E. coli* can be divided into four phylogenetic groups: A.B1, B2 and D. The virulent extra-intestinal pathogens are usually found in classes B2 and D [21]. In the last decade, *E. coli* sequence type (ST) 131 has emerged as a pandemic uropathogenic *E. coli* causing community and hospital-acquired infections especially urinary tract infections [22]. *E. coli* ST 131 is also represented among resistant isolates in companion animals. A European study determined the presence of *E. coli* ST131 which mostly produced CTX-m-15, comprising 5.6% ESBL-producing isolates recovered from companion animals [23].

Enterobacteriaceae confer antibiotic resistance by producing enzymes such as carbapenemases. The carbapenemases modifies the carbapenems through the hydrolysis of antibiotic and has been defined into different classes using Ambler classification system. The resistance in *Enterobacteriaceae* is found within Ambler class A (KPC—*K. pneumonia*Carbapenemase), class B(metello- β-lactamase) and class D (OXA-oxacillinase) [24]. KPC-type β-lactamases, are the most frequent cause of carbapenem resistance in the United States and has spread rapidly to Europe [25]. The most recent class B enzyme identified is the New Delhi Metallo-β-lactamase (NDM-1) in 2009. These enzymes are frequently found in *K. pneumoniae* and *E. coli.* The majority NDM producing isolates are found in Indian subcontinent [26].

Acinetobacterbaumanni has gained recognition as a major nosocomial pathogen in recent years predominantly affecting immunocompromised or critically ill patients. It causes a wide range of infections including pneumonia, bacteremia and infections of skin, bone, urinary tract and central nervous system [27]. The remarkable ability of *A. baumannii* to up-regulate or acquire antibiotic resistance determinants makes the bacterium a significant nosocomial pathogen. Resistance to cabapenems has been reported worldwide, including Australia [28, 29]. Many genotypes conferring such resistance have been found to belong to European clones (EU) I.11 or111 [28]. Although several molecular mechanism were responsible for conferring cabapenem resistance, the most common is the production class D β –lactamases, OXA-type carbapenemases. Class B metallo-beta-lactamases (such as IMP-, VIM-and SIM types) are occasionally identified in *A. baumannii*which have acquired these resistant determinants via class 1 interogons [30]. Alternation of penicillin-binding proteins and loss of outer membrane proteins, efflux pump mechanisms and other β-lactameses are also found in *A baumannii* [31, 32]. Researchers in Australia favor the view that farm animals may be the reservoir of resistance mechanisms and the current evidence of spread of most recent and notorious carbapenem resistance genes demonstrate that need for increased surveillance of antibiotic usage in veterinary and farm animals as well as in humans [8].

PATTERNS OF HAIs

Bloodstream Infection

Bloodstream infection remain the life threatening occurrence and is most commonly associated with the presence of central vascular catheter but may also be associated with gram-negative infection in any other areas of the body, such as the lung, genitourinary tract or abdomen. Approximately 30% of hospital acquired bloodstream infections in ICUs in United States are due to gram-negative organisms, although this proportion is lower when hospital–wide data are examined [11, 10]. Give an adequate portal of entry, almost any gram-negative organism can cause bloodstream infection; however, the most common organisms include *Klebsiella*, *Escherichia coli*, *Enterobacter* species, *P. aeruginosa* and lately *A. baumannii.* Antimicrobial resistance among organisms that cause hospital acquired infections is an emerging problem, particularly resistance against extended-spectrum cephalosprins and carbapenems .For example, of bloodstream isolates *Klebsiellapnreumoniae* from hospitals throughout the United States, 27.1% (from 483 isolates tested) were resistant to third generation cephalosporin's and 108% (from 452 isolates tested) were resistant to carbapenems [10]. Higher rates of resistance are reported from parts of Europe [33].

The most recent challenge has been the spread of carbapenemase-producing Enterobacteriaceae [34]. The beta-lactamase responsible for this phenotype, also known as *K.pneumoniae*carbapenemase, or KPC, confers reduced susceptibility to all cepahalosporins (including) cefepime), monobactams (aztreonam), and the cabapenems[34]. arbapenemase producing Enterobacteriaceae have now been identified in hospitals in at least 20 states in the United States, as well as in other parts of the world, including South America, Israel, China, and, less commonly, Europe [34]. The genetic relatedness of the strains responsible for outbreaks within and between countries highlights the importance of strict infection control to prevent ongoing dissemination [35,]. These beta-lactamases are encoded on mobile genetic elements, mostly plasmids and transposons, which probably explains their spread among gram-negative genera. Furthermore, they often coexist with other resistance genes, including the most widespread of the ESBLs (*bla*CTX-M-15gene), aminoglycoside plasmid-mediated quinolones-resistance genes (qnrA and qnrB) [34], thus leaving the physician with few therapeutic options. As has been described for nonfermenting gram-negative organisms, *K, pneumoniae* strains that are resistant to all currently available antibiotics, including the polymixins ,have been reported[33].

Prevention of bloodstream infections associated with central catheters is of paramount importance. Adherence to evidence-based interventions has proved highly successful, and hospitals worldwide should be adopting such cost effective, preventive measures. Evidence is also emerging in support of other interventions, such as the use of catheters impregnated with antiseptic, an antibiotic, or both [36,37], or the use of chlorhexidine impregnated dressings; however, when the described interventions for best practice are adhered to, the cost effectiveness of these interventions is less clear [38].

Nosocomial Pneumonia

Hospital acquired pneumonia is the most common life- threatening hospital acquired infection, and the majority of the cases are associated with mechanical ventilation. Ventilator-associated pneumonia occurs in approximately 10 to 20 % of patients who are on ventilators for longer than 48 hours and is associated with significant increases in length of hospital stay, mortality, and costs [39]. Gram-negative organisms predominate in hospital-acquired pneumonia, particularly *P. aeruginosa*, and the *A. baumannii* and the Enterobacteriaceae [11]. Between 1986 and 2003, acinetobacter species were the only gram-negative organisms that increased significantly as a cause of pneumonia in ICUs in the United States [11]. Unfortunately, the resistance of these organisms to antibiotics, particularly to carbapenems, has posed important

therapeutic challenges. In a recent survey, 26.4% of 679 *P. aeruginosa* isolates and 36.8% of 427 *A. baumannii* isolates that caused ventilator-associated pneumonia were resistant to carbapenems (imipenem or meropenem) [10]. Similar data have been reported from other parts of world, with countries such as Greece reporting rates of carbapenem resistance up to 85 % among ICU isolates [33].0f greatest concern are reports of infections caused by organisms that are resistant to all currently available antibiotics, including the polymixins[40, 41]. A more recent clinical entity that physicians need to be aware of is health care – associated pneumonia that is cases of pneumonia acquired in the community by patients who have had direct or indirect contact with a health care or long-term care facility and are subsequently hospitalized. Such patients are more likely to have a coexisting illness and to receive inactive empirical therapy and are greater risk for death than patients who have true community-acquired pneumonia [42, 43]. As a consequence, antibiotics with broad spectrum coverage-particularly those with activity against *P. aeruginosa*, other multidrug-resistant gram negative bacilli, and drug resistant *Staphylococcus aureus*, should be considered for patients who have defined risk factors and who present to the emergency room with pneumonia[44-46,]. In order to minimize the overuse of broad-spectrum antibiotics, further research is required to determine the true value of each of these risk factors for resistant bacteria [47]. At the same time when the patient is severely ill, the administration of empirical antibiotics therapy should not be delayed on account of the diagnostic procedures[45].

Nosocomial Urinary Tract Infection

Gram–negative organisms predominate in hospital-acquired urinary tract infections (UTIs), almost all of which are associated with urethral catheterization. After the second day of catheterization, it is estimated that risk of bacteriuria increases by 5 to 10 % per day. The majority of cases bacteriuriaare asymptomatic, and most effective management is removal of the catheter rather than antibiotic treatment. In rare cases, local and systemic complications ensues, and antibiotic treatment should be initiated for asymptomatic bacteriuria in patients who are about to go urologic surgery or implantation of prosthesis [46]. Such therapy should also be considered in immunocompromised patients. Bloodstream infections appear to be a well-defined but are rare complication of catheter-associated UTIs [47].

Researchers in U.S .have shown that *E. coli* is the most common etiologic gram-negative organism, followed in descending order of frequency by *P. aeruginosa*, *Klebsiella* species, Enterobacterspecies, and *A baumannii*[10]. Uropathogenic *E. coli* strains infect the urinary tract through a range of mechanisms, including specialized adhesions, fimbriae, biofilm, and aversion of host responses [48]. The emergence of resistance to quninolones and extended –spectrum cephalosporins remains a considerable challenge, since these agents are often used as first-line therapy. The traditionally, SHV-type and TEM-type ESBLs have predominated among hospital-acquired organisms, and this is still the case in the United States. The epidemiology of ESBLs is changing, however, and CTX-M type ESBLs is becoming more common worldwide. In particular, CTX-M-15 is most wide spread, and this β-lactamase has frequently been associated with auropathogenic *E. coli* clone known as sequence type 131 [49]. Unfortunately, the plasmids carrying these ESBL genes often carry resistance determinants targeting fluroquinolones as well. To reduce the morbidity associated with hospital-acquired UTIs and prevent the dissemination of drug resistant gram-negative organisms, adherence to evidence- based prevention guidelines is strongly recommended. Until further data are available, the use of antibiotic-impregnated or silver-coated catheters is not recommended [50].

CHOICE OF ANTIBIOTICS IN HAIs

The therapy of MDR gram-negative bacteria creates a challenge to clinicians. The class of polymixins mostly polymixin B and polymixin E (colistin), has gained a principal role in the treatment of most problematic MDR

gram-negative pathogens, such as *P. aeruginosa, A. baumannii, K. pneumoniae and Stenotrophomonasmaltophila*[9]. Tigecycline, the first representative of the new class of glycylclines, hold promise in infections from MDR *K. pneumoniae*carbapenemase(KPC) and ESBL-producing strains and Enterobacteriaceae with various mechanisms of resistance. The in vitro activity of tigecycline against *Abaumannii* makes it a tempting option, as it is the most active compound against MDR strains along with colistin [9]. Doripenem a member of carbapenems seems to possess a lower potential for resistance selection and a more favorable pharmacokinetic profile when given as an extended infusion [9].

CONCLUSIONS

Hospital acquired infections (HAIs) are main challenge to medical fraternity and to patient safety. The emergence of multidrug-resistant Gram –negative bacteria creates serious problems in the treatment of HAIs. Many researchers advocate that farm animals may be the reservoir of resistance mechanisms and the current evidence of spread of carbapenem resistance genes demonstrate the need for surveillance of antibiotic usages in animals and in humans (8).

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